These references provide no teaching or motivation for any form of pharmaceutical carrier that would allow sufficient bioavailability of HGF in a treatment by injection that is intravenous, intraarterial, intraperitoneal, subcutaneous, muscular or by other infusion. Quite to the contrary, the inclusion of the matrigel or polyvinyl carrier component in each of these references would exclude the compositions in these references from reaching the claimed invention.

The remaining reference from the previous Office Action, Zarnegar et al., does not teach any form of delivery of HGF in any form of treatment and in fact, teaches away from the claimed invention. Zarnegar et al. is a generalized teaching on the cellular activity of HGF *in vivo* when present in naturally occurring amounts. The Zarnegar et al. reference is predominantly devoted to disclosing findings related to the physiological function of HGF in normal and pathological conditions and its naturally occurring distribution in certain human tissues and experimental animals.

Zarnegar et al. does not teach delivery of HGF by local sustained release action from a matrigel or polyvinyl plug, but one of ordinary skill in the art, upon considering this teaching in Rosen et al., Grant et al., and Bussolino et al. would not be motivated toward a treatment by injection that is intravenous, intraarterial, intraperitoneal, subcutaneous, muscular or by other infusion, and upon reading Zarnegar et al., would look away from considering making any such modification to the teachings in these references.

It is well known in the pharmaceutical arts that sustained slow release of any agent can be discontinued if complications arise and that this level of control is not possible in a treatment by injection that is intravenous, intraarterial, intraperitoneal, subcutaneous, muscular or by other infusion. In addition, relatively much larger amounts of the active agent must be injected to reach sufficient bioavailability of the active agent when using treatment by injection that is intravenous,

intraarterial, intraperitoneal, subcutaneous, muscular or by other infusion as opposed to local delivery by sustained release.

Zarnegar et al. was published in 1993 contemporaneous with Rosen et al., Grant et al., and Bussolino et al. and shortly before the original filing date of the instant application. Based on the teaching of Zarnegar et al., one of ordinary skill in the art would not be motivated to modify the teaching of slow sustained release toward a treatment by injection as the bioactivity of HGF was not fully understood and the danger of potential side-effects were apparent.

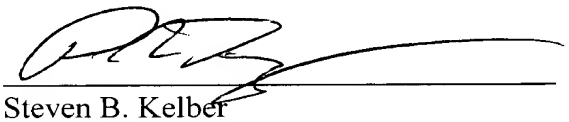
Zarnegar et al. states this in the first full paragraph on page 182 as such: "As is the case for many growth factors, HGF-SF's effect on its target cells is pluripotent in nature; it can induce a variety of different cellular responses which are highly regulated. Abnormal expression and secretion of HGF-SF or its receptor c-*met* may lead to neoplasia or tumor meta-stasis."

Accordingly, upon reading Zarnegar et al., one of ordinary skill in the art would not be motivated to move beyond the localized and controlled environment in the sustained release method disclosed in Rosen et al., Grant et al., and Bussolino et al. The claimed invention including HGF and the claim designated carrier is both novel and non-obvious in light of these references.

Applicants assert that this application is now in condition for allowance and therefore request favorable consideration. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PIPER RUDNICK LLP



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